IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
DUCRAY ET AL.
APPLICATION NO: 10/501,495
FILED: JULY 14, 2006
FOR: AMIDOACETONITRILE DERIVATIVES

Art Unit: 1626
Examiner: Sackey, Ebenezer O
Confirmation Number 8264

DECLARATION

I, Ronald Kaminsky, a citizen of Germany residing in Lugnorre, Switzerland, make the following declaration:

1. I am diplom biologist, a Doctor of agricultural Sciences and a Dozent for Zoology

University of Cologne, Germany: Diploma in biology,
Dissertation (Dr.sc.agr.) in agricultural sciences: summa cum laude
Habilitation at the University of Cologne
Venia docendi for Zoology, University of Basel

2. Since 1999, I have been employed by NOVARTIS ANIMAL HEALTH Inc., a Swiss corporation, with offices at Basel, Switzerland, and the Assignee of the above referenced patent application. As Head of Parasitology at the Novartis Centre de Recherche Sante Animale, St-Aubin, Switzerland, I am currently leading the combined groups of Screening, Rodent Models, Companion Animal Parasiticides and Farm Animal Parasiticides. I am responsible for the parasiticidal screening and biological evaluation of chemical substances in the field of Animal Health.

My employment history is as follows:

Since 1999 Novartis Animal Health, St. Aubin, Switzerland
Head of Parasitology, Biosafety officer

1992 - 1999 Swiss Tropical Institute, Basel, Switzerland
Senior Scientist: project leader for chemotherapy of infectious protozoa and for drug resistance projects
Teaching at University of Basel: Molecular Parasitology, Cell Biology

1986 - 1992 Laboratory for Research on Animal Diseases (ILRAD), Kenya
Scientist: Project leader for chemotherapy of pathogenic trypanosomes

1985 - 1986 University of Massachussetts, Amherst, USA

Postdoctoral research fellow at Center of Parasitology

1983 – 1984 Medical Dept., University of Göttingen, Germany
Postdoctoral research assistant at the Institute of Tropical Hygiene

3. I am author or co-author of approximately 100 peer reviewed scientific papers, a selection of recent key papers is given below:

- P Mäser, C Sütterlin, A Kralli, R Kaminsky: A Nucleoside Transporter from Trypanosoma brucei involved in drug resistance. SCIENCE 285 (1999) 242-244
- R Kaminsky, B Nickel, A Holy: Arrest of Trypanosoma brucei rhodesiense and T. brucei brucei in the S-phase of the cell cycle by (S)-9-(hydroxy-2-phosphonylmethoxypropyl)adenine ((S)-HPMPA). Molecular and Biochemical Parasitology 93 (1998) 91-100
- P Mäser and R Kaminsky: Identification of three ABC transporter genes in Trypanosoma spp. Parasitol. Res. 84 (1998) 106-111
- P Mäser, D Vogel, C Schmid, B Räz, R Kaminsky: Identification and characterization of trypanocides by functional expression of an adenosine transporter from Trypanosoma brucei in yeast. J Mol Med 79 (2001) 121-127

and I am an author or co-author of about 20 review articles, most recent ones are listed below:

- R Kaminsky. Drug resistance in nematodes: a paper tiger or a real problem ? Current Opinion in Infectious Diseases 16 (2003) 559-564
- D Kerboeuf, W Blackhall, R Kaminsky, G von Samson-Himmelstjerna. P-glycoprotein in helminths: function and perspectives for anthelmintic treatment and reversal of resistance. Int. Journal of Antimicrobial Agents 22 (2003) 332-346
- R Kaminsky: Miltefosine. Current Opinion in Investigational Drugs 3 (2002) 550-554
- P Mäser, A Lüscher, R Kaminsky. Drug transport and drug resistance in African trypanosomes. Drug resistance updates 6 (2003) 281-290
- R Kaminsky and P Mäser: Drug resistance in African trypanosomes. Current Opinion in Anti-infective investigational Drugs 2 (2000), 76-82
- R Kaminsky: Associate-editor of "Handbook of Animal Models of Infection"; editor of volume IV "Parasitic infection models"(1999) Academic Press

4. I am familiar with the class of compounds described in the Ducray et al. U.S. Application No. 10/501,595 because I received from the inventors substances selected from the chemical scope of the Ducray et al. application and tested them against parasites on animals.

5. I am an inventor or co-inventor of 5 patent applications related to chemicals that have parasiticidal activity.

6. I am familiar with the pending Office Action for the above referenced patent application that was mailed on May 5, 2006.

7. I have been asked to reviewed U.S. Patent 6,239,077 Andoh et al. I studied the Andoh et al. reference carefully and would like to comment on my findings as follows:

The description of the activity spectrum of the compounds disclosed by Andoh et al. starts on line 44 on columns 26 and ends line 52 on column 27.

The initial part of this paragraph reads:

> *"The agricultural and horticultural insecticide containing the aminoacetonitrile derivative of the formula (I) of the invention as an active ingredient is suitable for controlling various pests in agriculture, forestry, horticulture, stored products as well as sanitary vermin or nematoda which are harmful for paddy rice, fruit trees, vegetables, other crops and flowers."*

From this paragraph I can only conclude that the field of use relates to the protection of pests which damage plants.

This became even more true when I read the subsequent huge list naming specifically the various pest species which are either plant injurious insects or soil nematodes.

The paragraph starting on column 27, line 41 makes this undoubtedly clear. It reads:

> *"The agricultural and horticultural insecticide containing the aminoacetonitrile derivative of the formula (I) of the invention has remarkable controlling effect on the above-mentioned pests harmful to paddy field crops, farm crops, fruit trees, vegetables, and other crops and flowers so that treatment of paddy field water, stems and leaves or soil, such as paddy field, farm, fruit trees, vegetables, other crops, and flowers in a good timing when emergence of pests is expected and before emergence of pests or after their emergence is confirmed will exhibit the desired effects of the agricultural and horticultural insecticide of the present invention."*

In the next paragraph it is stated that the compounds are formulated according to conventional methods.

On column 29, lines 1 to 7 specify how one can achieve control, i.e. how said formulations are applied. This paragraph reads:

> *"In order to control various pests, the agricultural and horticultural insecticide of the present invention can be applied in an amount effective to prevent insect damages as it is or suitably diluted with or suspended in water or the like, to crops on which emergence of the pests is expected or to the place where emergence of the pests is undesirable. "*

This paragraph is another clear indication that the described invention deals with nothing but plant protection. In the next paragraph it is explicitly stated how many kilograms one has to apply to a specific area.

I have also studied the Test Examples 1 and 2. Test Example 1 deals with Diamondback Moth (*Plutella xylostella*), which is an agricultural pest on plants from the family *Brassicaceae* (*Cruciferae*) : Chinese broccoli (*Brassica oleracea var. alboglabra*), Cauliflower (*Brassica oleracea var. botrytis*), Cabbage (*Brassica oleracea var. capitata*), Brussel Sprouts, (*Brassica oleracea var. gemmifera*), Broccoli (*Brassica oleracea var. italica*), Chinese cabbage (*Brassica rapa var. pekinensis*), Radish (*Raphanus sativus*), Watercress (*Rorippa nasturtium-aquaticum*), and Mustard (*Sinapsis alba*). Host plants also include several ornamentals, such as : Wallflower (*Cheiranthus cheiri*), Candytuft *(Iberis umbellata*), Alyssum (*Lobularia maritima*), and Stocks (*Matthiola longipetala*). An important reservoir for the species are Wild mustard (*Brassica kaber*). This caterpillar has absolutely nothing to do with any pest that infests animals.

Test Example 2 deals with Smaller Tea Tortrix (*Adoxophyes species*). The Smaller Tea Tortrix is also known as the Summer Fruit Tortrix Moth and is one of the most devastating pests in apples and pears. The upper wings are light ochreous brown with two darker patterns of a widening strip. Head, thorax and legs whitish brown. The hindwings are light grey. The females differ a bit from the males: they are bigger, the patterns on the front wings are darker and the hind wings are brownish grey. The males will reach a wingspan of 17 to 19 mm, the females up to 22 mm. This moth is a gain a plant infesting pest that has absolutely nothing in common with any animal pest.
From the description of both Test Examples it becomes obvious that the insect has to be cultivated on plant material.

There is absolutely nothing in the Andoh et al. reference that could lead to the assumption that these compounds could be successfully used for combating pests in or on warm-blooded animals. There is even not any hint that allows one to conclude whether these compounds are toxic or tolerated by warm-blooded animals. Even if they would be suitable for veterinary use, a skilled person would have no guidance how to use them, *i.e.* in what kind of formulation, in which dosage and with which dosage regime.
Thus, from my perspective, Andoh et al. teach compounds that kill parasites that live on plants or in soil but do not guide to any veterinary aspect.

8. I also studied the Ducray et al. application No. 10/501,595 and concluded the following: It is my understanding that Ducray et al. provide a class of compounds suitable for veterinary use. In the fourth paragraph on page 13 of the patent description Ducray et al. state that these compounds

"...are characterized by a particularly broad activity spectrum and are valuable active ingredients in the field of pest control which are well tolerated by warm-blooded species,

fish and plants, including in particular for controlling endo- and ectoparasites which parasitize animals."

In the next paragraph the inventors illuminate the activity spectrum by providing a long list of parasites that are affected by these new compounds. This list embraces parasites that affect plants and typical parasites that either parasitize on the top (fur / skin) or inside (in the body) of warm-blooded animals. I found typical representatives of external parasites such as *Ctenocephalides felis* and *Ctenocephalides canis*, which are nothing but cat and dog fleas; *Xenopsylla cheopis, Pulex irritans, Dermatophilus penetrans*, which represent lice; and ticks like *Boophilus*, *Amblyomma*, *Anocentor*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes*, *Rhipicentor*, *Margaropus*, *Rhipicephalus*, etc. A whole paragraph deals with important internal parasites. It starts with the following statement:

"The compounds are particularly active against helminths, among which the endoparasitic nematodes and trematodes can be the cause of serious diseases in mammals and poultry, e.g. in sheep, pigs, goats, cattle, horses, donkeys, dogs, cats, guinea pigs and ornamental birds. Typical nematodes of this indication are: ...".

On pages 16 and 17 the inventors describe how the compounds can be formulated and applied in order to achieve the beneficial result in animals. It is also described with which kind of further parasiticides these compounds could be mixed in order to broaden the activity spectrum or improve it.

The Ducray et al. application provides the following biological examples:

Example 1. In vivo test against *Trichostrongylus colubriformis* and *Haemonchus contortus* in Mongolian gerbils (*Meriones unguiculatus*) by peroral administration.
This test demonstrates the pronounced anthelmintic activity of these new compounds. The parasitic helminths belong to the three groups (1) Nematodes or round worms, (2) Cestodes or tapeworms and (3) Trematodes or flukes. Certain helminths infest the intestinal tract of the host animal, while others of the species *Haemonchus* and *Ostertagia* are parasitic in the stomach and those of the species *Dictyocaulus* are parasitic in the lung tissue. Parasites of the families *Filariidae* and *Setariidae* may be found in the internal cell tissue and in the organs, e.g. the heart, the blood vessels, the lymph vessels and the subcutaneous tissue. A particularly notable parasite is the heartworm of the dog, *Dirofilaria immitis*. Helminths cause severe symptomps and can lead to the death of the infested animal.

Example 2. Action against L_1 larvae of *Lucilia sericata*. *Lucilia sericata* is one of the facultative parasites which causes myiasis in animals, and rarely in humans as an ectoparasite. Infestation in humans and domestic herbivorous animals occurs in wounds,

mouth, eyes, and nose. It causes itching, pain, inflammation, secondary bacterial infections, eosinophilia, and erythema.

Example 3. Acaricidal action against *Boophilus microplus* (Biarra strain).
Example 4. In vitro activity against fed *Boophilus microplus* females (Biarra).
Boophilus microplus is a one-host tick distributed throughout much of the world. It is found in Mexico, much of Africa, Central and South America, Madagascar, Taiwan, and Australia. It infects a variety of animals, including cattle, sheep, goats, and horses, but it seems to prefer cattle. It is considered to be the most serious ectoparasite of cattle. This tick transmits several diseases known collectively as 'tick fever.' These diseases include babesiosis (caused by the apicomplexans *Babesia bovis* and *B. bigemina*) and anaplasmosis (caused by the rickettsia *Anaplasma marginale*). Members of this genus have also been implicated as vectors for several viral hemorrhagic fevers (e.g., Crimean-Congo hemorrhagic fever).

Example 5. In vitro activity against nymphs of *Amblyomma hebraeum*.
Amblyomma hebraeum is a hard tick that infests livestock and wildlife. This tick can leave large wounds that may become infected by bacteria or infested by screwworms. It can also transmit heartwater (infection by *Cowdria ruminantium*) to ruminants. Its larvae transmit tick typhus (infection by *Rickettsia conorii*) to humans. Immature ticks feed on small mammals, ground–feeding birds, and reptiles.

Example 6. Action against *Dermanyssus gallinae*.
Dermanyssus gallinae is a bloodsucking mesostigmatid mite, also known as the red mite, and it is a blood feeder of poultry. This poultry red mite or chicken mite, is the most important haematophagous poultry ectoparasite. Parasitism of this haemotophagous chicken mite is demonstrated through disturbance of poultry, irritation, anemia, transfer of diseases, reduced laying ability, and sometimes even death.

From the whole contents of the Ducray et al. application and especially if I take into account the biological examples and the use claim, I have the impression that this patent application is basically directed to a class of compounds which are well tolerated by warm-blooded animals and exhibits excellent activity against a broad spectrum of external and internal parasites on animals.

These findings could have never been predicted by anyone skilled in the art by simply analyzing the Andoh et al. reference. There is absolutely no motivation for testing these plant protection compounds against parasites in or on animals.

9. All-in-all, I take the position that one of ordinary skill in the art would not have reasonable expectation that the compounds taught in Andoh et al. would be effective against parasites in mammals. One of ordinary skill in the art would not know without conducting tests on a mammal that the compounds of Andoh et al. could be administered to a mammal in sufficient concentration to kill the parasites and yet not hurt the mammal. One of ordinary skill in the art would not know, *apriori*, that the Andoh et al. compounds would NOT be degraded after the compounds enter the mammal's body. It was possible that the enzymes in the blood or in the liver would degrade the Andoh et al. compounds into chemicals that lack parasiticide activity. In addition, one of ordinary skill in the art would not know without conducting tests that the Andoh et al. compounds would not be toxic to the mammal to which the compounds are administered but would be effective at killing the parasites.

10. It is for these reasons that the results for the compounds claimed were surprising and unexpected.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and correct, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 10th day of July, 2006.

Ronald Kaminsky